DMID Perspective for Conducting Clinical Trials

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Guiding Principles for Conducting Clinical Trials

- Protection of human subjects
- Conduct studies according to GCP
- Generation of robust data

Framework for Conducting Clinical Studies

- US Government regulatory authorities
  - US FDA (Code of Federal Regulations)
    - Investigational New Drug Application (IND)
    - Biologics License Application (BLA)
    - New Drug Application (NDA)
- International Conference on Harmonisation (ICH)
- NIH Terms of Award (TOA) for grants and cooperative agreements
- European Regulatory Authorities (National Competent Authority, EMEA, Medicines and Health Products Regulatory Agency)
- In-Country regulatory authorities

DMID Perspective on Conduct of Studies under US IND

- Statutory requirement for use of investigational products in the US
- Human subjects risk level
- Vulnerable population
- Impact of study on public health policy
- Product development feasibility

What is an IND?

- FDA authorization to conduct clinical research using an unlicensed product or off-label use of licensed products
- Allows transport of unlicensed drugs for clinical study

When Does FDA Exempt a Drug from IND?

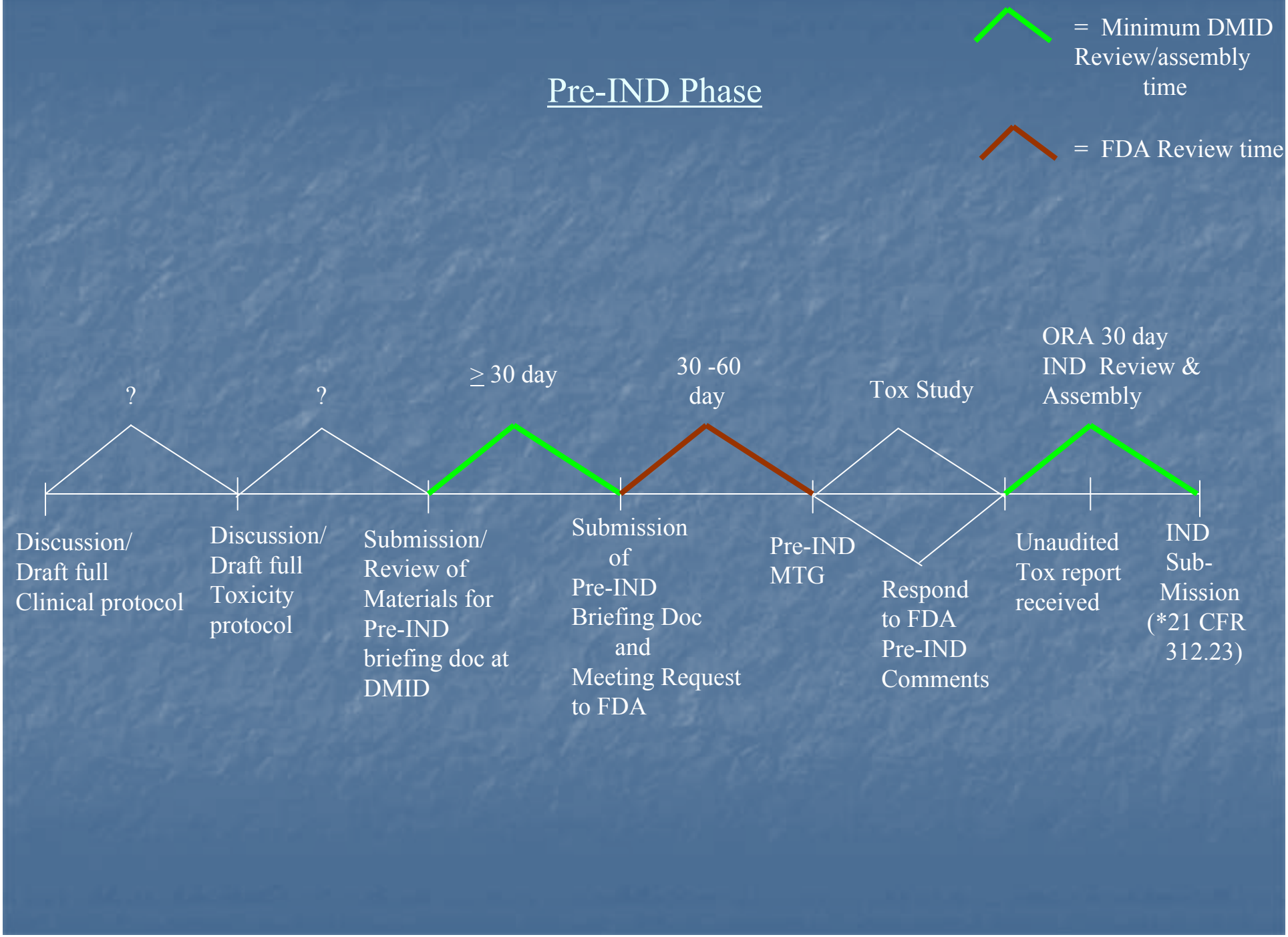
- If the product is lawfully marketed in the US and
- The study meets all of the following:
  - Not intended to be reported to the FDA as a well-controlled study in support of a labeling change
  - Not intended to support change in advertising
  - Route of administration, dose or patient population does not result in increased risks
  - Study is conducted in compliance with requirements for IRB and informed consent

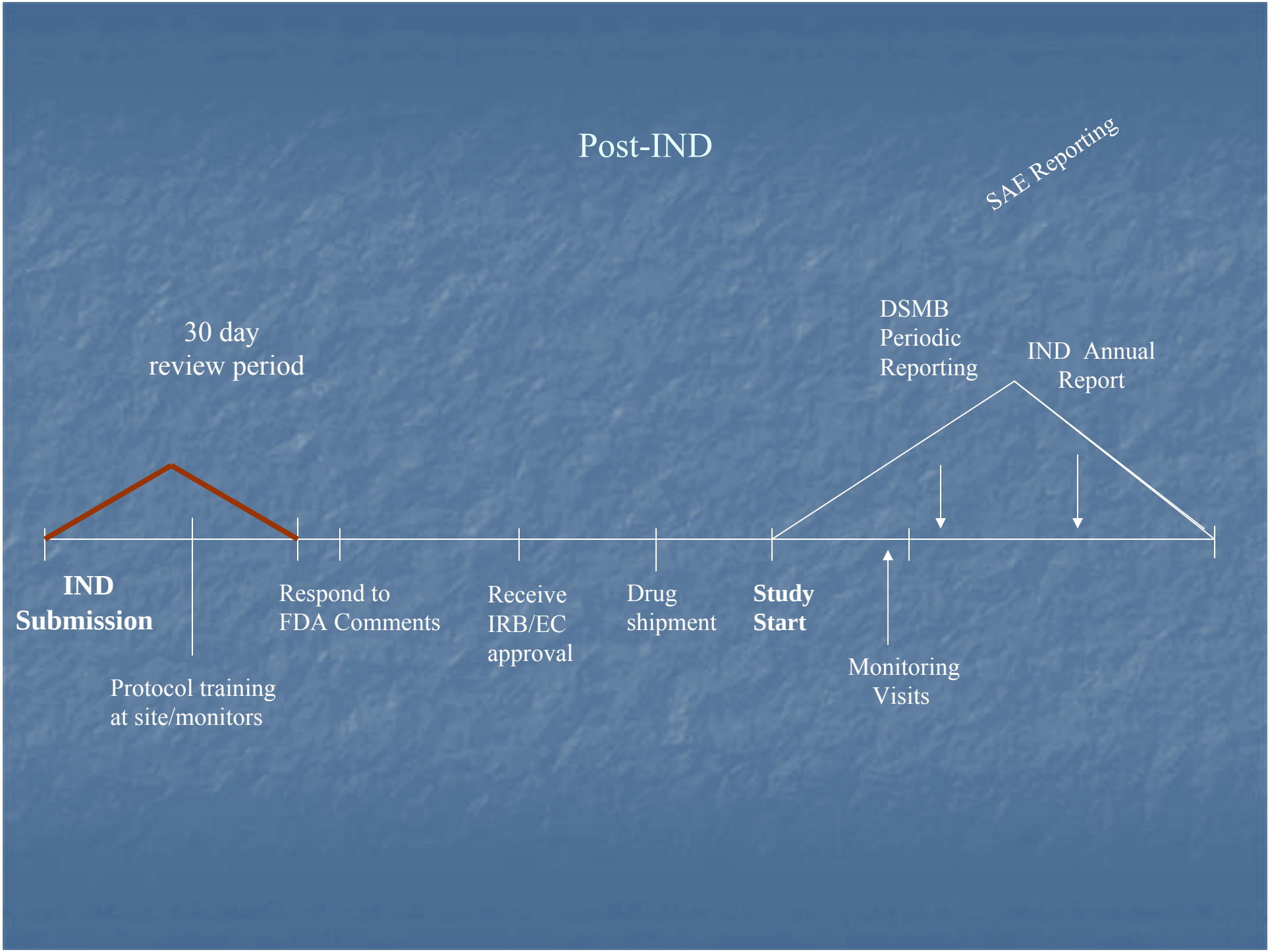
Considerations for DMID-Supported Clinical Research

- Review and approval of protocol by DMID
  - Scientific review (Program)
  - Regulatory and product review (ORA)
  - Protocol, consent form, safety monitoring plan review (OCRA)
- Drafting of Clinical Terms of Award to ensure adequate conduct and safety oversight
  - Safety monitoring plan
  - Conduct of study under IND
  - GCP compliance
  - Quality assurance audit
- Human subjects protections assurance (FWA)
- Development of Clinical Trials Agreement for studies in DMID-contract networks

Overview of DMID Process for IND Studies Where DMID is the IND Sponsor

Pre-IND Phase




Post-IND
SAE Reporting
30 day
review period
DSMB
Periodic
Reporting
IND Annual
Report
IND
Submission
Protocol training
at site/monitors
Respond to
FDA Comments
Receive
IRB/EC
approval
Drug
shipment
Study
Start
Monitoring
Visits

Required Elements for Review

- Summary Chemistry/Manufacturing/Controls (CMC) information if not U.S. licensed product
- Clinical protocol and Investigator's Brochure
- Previous human experience (safety/efficacy) at route, dose, regimen, and population for individual and/or combination therapies
- Non-clinical data to support safety of drug at route, dose, regimen, and population for individual and combination therapies
- Non-clinical data to support proof of concept activity/efficacy

Contents of IND (21 CFR 312.23)

- Introductory statement and general investigational plan
  - Rationale for study
  - Indications to be studied
  - General approach to be used in evaluating drug
  - Studies planned for the year and # subjects to receive drug
  - Any risks of particular severity or seriousness anticipated based on preclinical or clinical finding with this drug or related drugs
- Previous human experience
- Investigator's Brochure
  - Description of drug
  - Summary of PK and toxicity data in animals and humans
  - Summary of information related to safety and effectiveness in humans
- Description of possible risks
- Protocol for Clinical Use
- Chemistry, Manufacturing and Control Information (CMC)
  - Description of drug substance and drug product
- Curriculum vitae for Investigators
- 1572 identifying sites/subinvestigators
- Documentation of study drug accountability and handling
- Case Report Forms (CRFs)
- Labels

Challenges for Clinical Research

- Conducting studies in endemic areas
  - Role of FDA in studies with no US commercial interest
  - Determination of relevant endpoints
  - Evaluation in complex background of therapies and concomitant diseases
  - High degree of sensitivity to changing public health policies
- Source of products to be studied
  - Use of Good Manufacturing Practices (GMP)
- Import/export of unlicensed products
- Meeting NIH requirements for diversity of gender, ethnicity and age